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A CASE OF ACUTE LEUKÆMIA PRESENTING SOME INTERESTING FEATURES.[1]

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The accompanying case might not be deemed worthy of report because of the incompleteness of the record were there not very special features of interest that demand its publication. The patient was in the writer's wards of the Episcopal Hospital, in the spring of 1899, for thirty days prior to her death.

She was admitted with symptoms which, several inspections of the blood showing evident leukopænia, caused the diagnosis of scurvy to be made. These were: Spongy, hemorrhagic gums, with looseness of the teeth, fetid breath and furred tongue, an anæmic appearance, and a tendency to nose-bleed. The patient had been debilitated since the birth of her last child, three months before, and the above symptoms had since developed. Appropriate treatment for scorbutus was ordered, and but little further attention was paid to the case until she was well into what appeared to be an attack of typhoid fever.

The history is as follows:

Ann S., aged twenty-eight years; birthplace, Philadelphia; occupation, housework. Admitted to the Episcopal Hospital on April 11, 1899. Died on May 11, 1899.

Family History. Father said to have died of heart disease; mother of insanity. Otherwise, family history negative.

Previous History. Had measles when a child. No other infectious disease. Fairly healthy until lately, save that she had had a bad diarrhœa after the birth of one of her children. No specific history; never had had chills and fever. Married for nine years; five children; last child born three months before admission. Had nursed child for one month. She was of slender build, and her complexion was said to have been always pallid.

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[1] Read before the Association of American Physicians, 1901.

Present illness began some two or three months before (about February, 1899), shortly after the birth of her child. Then the gums became swollen and bled easily. There has since been a tendency to nose-bleed, but no hemorrhage from other parts of the body. On admission it was noticed that the patient presented a rather anæmic and markedly ill-nourished appearance, which she said was habitual with her. There was a history of overwork and privation. The gums were much swollen, soft, and spongy, almost covering the teeth in places, and tended to bleed easily. There had been no salivation, and she had not taken calomel. The teeth were quite loose, and the breath very foul, the tongue swollen and furred. The heart sounds were enfeebled. No murmurs were present. Indications of enlargement of the external lymph glands were not evident, and the area of splenic dulness was little increased over the normal.

An inspection of the blood by Dr. Ghriskey, on several occasions during the first week of admission, invariably showed a diminished number of leucocytes, a number of fields having to be covered for one to be seen. Red corpuscles pale, not distorted. No estimation of red or white corpuscles was then made.

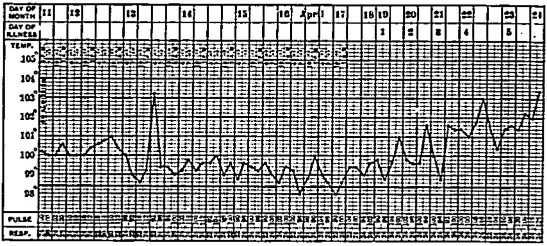
An astringent mouth-wash was prescribed. She was given a nourishing diet, containing such green vegetables as could be procured, and expressed meat juice and lemonade. Tincture of iron in syrup of lemon was prescribed, and a moderate amount of strychnine and whiskey ordered. Her temperature from the day of her admission is as recorded on the accompanying chart.

On the day of her admission (April 11th) and that following it varied from 100° to 101°, reaching 103.1° on the 13th, but subsequently, until April 19th, it did not exceed 100°. It had then begun to show a gradual rise suggestive of typhoid fever.

There was a great deal of typhoid fever in the wards at the time, and, coincident with the occurrence of the more or less characteristic temperature rise, it was suspected she was developing this disease. During the latter part of April her spleen, which on admission had not been palpable, became notably so. There was diarrhœa, and spots appeared on the abdomen, which superficially resembled the rash of enteric fever, and on May 2d the blood was reported to give a typical Widal reaction. The examination was made at the City Laboratory by Dr. A. H. Stewart from a dried specimen. Unfortunately, a second specimen was not sent. The abdomen had become distended, and there was marked tenderness in the right iliac region.

On May 7, 1899, it was noted that the rash had become general, and was unlike that of typhoid fever. The spots had much increased in size, and in places were becoming purpuric. Much aching was complained of in the extremities. The breath was highly offensive; the gums hemorrhagic and sloughing at several points. The heart sounds were much enfeebled. The spleen had become much enlarged, and was palpable two finger-breadths below the costal margin. The bowels were now very loose. An inspection of the blood, which had not been made since the first week of admission, showed an extensive leucocytosis, the large mononuclear cells prevailing. The report was: Leucocytes, 89,600; erythrocytes, 1,280,000; hæmoglobin, 25 per cent.

1


DAY OF MONTH
11
12
13
14
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April
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24
DAY OF ILLNESS
1
2
3
4
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TEMP.
105°
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103°
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100°
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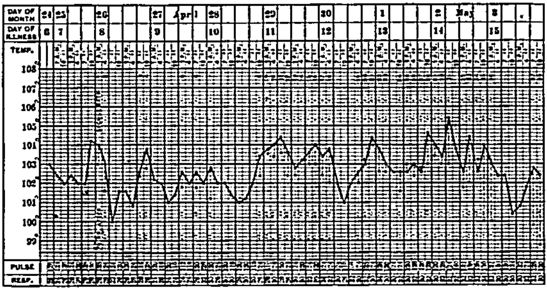
PULSE
RESP.

2


DAY OF MONTH
24
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April
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DAY OF ILLNESS
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TEMP.
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RESP.

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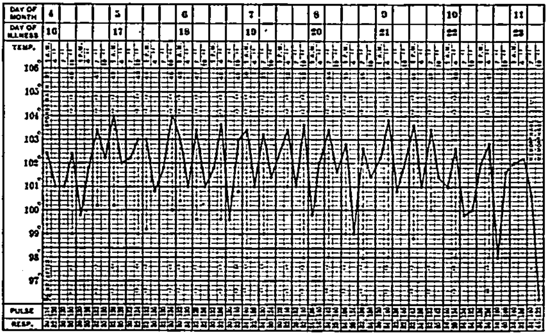
DAY OF MONTH
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DAY OF ILLNESS
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TEMP.
106°
105°
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98°
97°
PULSE
RESP.

Urine (catheterized specimen) turbid, contains numerous whitish flakes in suspension; reaction acid; albumin, marked trace to heat and acid; microscopically, numerous leucocytes singly and in clumps; granular and epithelial casts; many erythrocytes.

On May 9th it was noted that the purpuric rash had become more or less general, and tended to be confluent. Leucocyte estimation, 102,000.

11*th*. Leucocyte estimation made, but report missing. It is recalled that the count was considerably in excess of that of the 9th instant. She had a moderate hemorrhage from the bowel on the evening of the 10th, and a very large one the following morning. This was followed by symptoms of collapse. Despite repeated hypodermoclysis and other measures to restore her, she died on the evening of the 11th. In the last week of the illness diarrhœa was excessive.

Pathological Report by Dr. Robertson.

"Necropsy made six hours after death. Body of a rather emaciated woman. Purpuric spots over abdomen. Gums soft and swollen, and overlapped teeth more than normally. Subcutaneous fat greatly diminished. Musculature very poor.

"*Thorax.* Pericardial fluid normal in appearance and amount. Heart muscle pale and flabby. Valves and orifices normal. Weight, 256 grammes. Hemorrhagic foci on visceral layer of pericardium. Lungs: Calcareous nodule in apex of right lung, otherwise both are normal throughout.

"*Abdomen.* Stomach low in position. Kidneys: Both movable, the right one freely, the lower margin being on a level with the crest of the ilium, though some attachment still remained, being formed by the original perirenal tissue, which had been converted into a long band. Both kidneys pale on section, cortex widened, due to parenchymatous degeneration. Right kidney weighed 208 grammes; the left 256 grammes. Liver enlarged, rather pale, seat of parenchymatous degeneration. Spleen much larger than normal; weight, 432 grammes. Quite firm, unlike that which one finds usually in typhoid infection. Intestines: small bowel contained no ulcers. Peyer's patches distinctly visible, owing to numerous small pigmented spots within them. There were no signs of inflammation anywhere. The cæcum, ascending and transverse colon contained numerous deep, ragged ulcers, many with black, hemorrhagic sloughs, partly separated. A few of the ulcers were perilously near perforation, the serosa alone remaining, and this latter, on its peritoneal surface and the juxtaposing peritoneum, was congested and roughened. Blood clots were found in the large bowel. These ulcers did not resemble any typhoid ulceration that I have ever seen. They were very irregular in outline, and the erosion itself seemed to have progressed with varying degrees of rapidity in the same ulcer, hence the bosselated character, the unevenness of the base. The appendix, which was very long, contained two small ulcers near its tip. Unfortunately, no special study of the bone-marrow was made, the ribs and sternum alone being examined, and here it was normally of the red variety. The inguinal, mesenteric, and peribronchial lymph glands were enlarged and firm.

"Microscopically the ulcerated portion of the intestine appeared as follows: The mucosa was completely necrotic, and sections stained with thionin showed numerous micro-organisms, chiefly bacilli and streptococci. These had not penetrated very deeply into the submucosa. The lymphoid tissue had been infiltrated with plasma cells and large and small lymphocytes, so that as a matter of fact the normal adenoid tissue had been obliterated. Numerous plasma cells and mast cells were found scattered throughout the submucosa.

"*Spleen.* Vessels thickened. Malpighian corpuscles much less marked than normally, being apparently largely displaced by the very richly cellular parenchyma. Plasma cells and large endothelial cells seem to make up the large part of these. No bacteria could be found.

"*Lymph Gland.* The normal arrangement of a lymph gland is totally lost. It is very rich in cells, plasma and endothelial cells, the latter apparently descendants of the cells lining lymph vessels and spaces. Small and large lymphoid cells, aggregated into groups and surrounded by attenuated fibrous tissue, an approach to the normal, were only found at the periphery of the gland. No micro-organisms found.

"*Liver.* Parenchyma cells swollen and granular, the seat of parenchymatous degeneration. No increase of connective tissue or bile ducts, but here and there aggregations of lymphocytes and connective-tissue cells.

"*Kidney.* Seat of parenchymatous degeneration. Moderate congestion. About the glomeruli and between some of the tubules, particularly in the neighborhood of the glomeruli, were aggregations of plasma cells and large lymphocytes.

"*Heart.* An interstitial collection of plasma and connective-tissue cells, and a few lymphocytes. Muscle fibres stain well.

"From the histological examination the picture is that of any of the acute infections, plus the great increase of lymphocytes. The plasma cell has been found particularly in typhoid and diphtheria, but is met with in other infections also, though I scarcely think in as great numbers. How large a part they play in scurvy or acute leukæmia I do not know."

Specimens for microscopical examination were also submitted to Prof. Simon Flexner. The following is his report:

"*Intestine.* The section of intestine consists of a nodule equally within the mucous membrane and the adjacent tunics, including a portion of the omentum. The nodule occupies the whole of the mucous membrane as far as contained within the section, with the exception of a fragment of tissue at one end, in which the crypts of Lieberkuehn are still present. With this latter exception the entire tissue is degenerated and refuses to take the staining agents. The remainder of the membrane is made up of cells separated by a stroma, in some places coarse in texture and in others fibrillar. The degenerated edge goes over quite sharply into the cellular layer, and there the line of demarcation is occupied by brightly staining cells and intercellular tissue.

"As regards the preserved portion of the cellular infiltration, it consists of cells of large size, possessing vesicular nuclei, the latter being reticulated, and an abundance of protoplasm. Among these are small cells resembling lymphoid cells in all particulars. Many of these cells show karyokinetic figures. These figures are especially marked in the large cells described. They exist throughout the nodule, are about uniformly distributed, and in the preserved edge of the tissue, just below the degenerated tissue, are present as described. These dividing cells show all stages from the simple dividing aster to the completely divided nucleus; rarely four or five nuclei are found contained within a single cell. The infiltration described involves the mucous membrane and submucosa, so that no distinction can be made out in these two tunics. The muscular coat, on the other hand, is less uniformly affected, but in it are islands of cellular tissue, presenting the same characters as those of the mucosa and submucosa. The cells composing the nodules are made up chiefly of the larger cells described. Among these there is also evidence of karyokinesis. The peritoneal coat is very diffusely infiltrated with similar large cells, chiefly, although some of the smaller lymphoid cells are also present, and cell division is going on among these cells. The bloodvessels, chiefly of the muscular coat, show an increase of white elements, especially of larger white elements with single nuclei, and it is found that nodules in the muscular coat had developed about such bloodvessels and perhaps also about lymphatics. The type of large cell agrees with the type of large mononuclear leucocyte as found in the blood, and they may be considered as being alike, inasmuch as those within the vessels agree with those without the vessels. That the nodules have arisen, at least in part, by proliferation *in situ* is shown by the active karyokinesis.

"*Mesenteric Gland.* Section of this gland shows that it is not greatly enlarged. Upon microscopical examination there is seen hyperplasia of the entire gland, which largely obliterates the distinction between the cortex and medulla, and in which there are numbers of cells having the general characteristics of large mononuclear leucocytes. In these cells karyokinesis is also apparent.

"*Spleen.* Shows a considerable amount of yellow blood pigment. It is uniformly infiltrated with cells; rarely can a Malpighian body be made out. The cells are of the type of lymphocytes, the larger ones chiefly being represented. Cellular accumulations are found, especially in the pulp. Karyokinesis also appears in the large cells.

"*Liver.* The cells are granular. The capillaries contain a greatly increased number of white elements, which partake especially of the character of lymphocytes. In addition to which there are scattered nodules of cells surrounding branches of the hepatic veins especially, consisting of large lymphocytes admixed with a small number of small lymphocytes. These occupy the sheath of vessels and extend into the liver tissue and take in part its place. Karyokinesis is also to be seen among these cells.

"*Kidney.* Shows swelling and granular degeneration, and some fatty degeneration of the tubular epithelium. It also shows small hemorrhages into the tubules, and focal accumulations of the large mononuclear elements within the kidney substance, chiefly about the glomeruli.

"*Heart.* Section of heart muscle shows, first, an increase in fibrous tissue about the larger bloodvessels; second, focal accumulation of cells, chiefly of the type of lymphocytes between the muscle fibres. These accumulations are often elongated, adapting themselves to the spaces between the fibres. An occasional nucleus, such as are found in polymorphonuclears and an occasional red cell, are also found.

"*Diagnosis.* These sections come from an undoubted case of lymphatic leukæmia of the large mononuclear type. The bloodvessels contain greatly increased numbers of these mononuclear elements. From the bloodvessels they have escaped into various situations of the body, especially into the intestinal mucosa and submucosa, where they have developed with the production of leukæmic nodules."

A differential blood count was made for me by Dr. Thayer, of the Johns Hopkins Hospital, for which I here express my great indebtedness. It is as follows:

"The specimen of blood which you sent me is very remarkable. It is clearly an example of large-celled lymphatic leukæmia. I have seen similar bloods in two instances of very acute lymphatic leukæmia, in one associated with hemorrhagic and extensive areas of cutaneous gangrene. The type of blood is that which, in my experience, is associated with the most rapid and malignant type of lymphatic leukæmia. The two specimens were stained, one with Ehrlich's eosin hæmatoxylin, the other with the triple stain. In the first place the specimens stained badly. Whether with the triple stain or with other stains the ground substance between the different cells takes a distinct color, a slight, diffuse lilac stain in specimens stained with the triple stain, and a more reddish color in the eosin hæmatoxylin specimen. This is especially marked round about each leucocyte. The red corpuscles show moderate variation in size, a slight, though not great, poikilocytosis. No nucleated red blood-corpuscles were seen. There is a great increase in the number of leucocytes, which are almost entirely mononuclear. Many of these, however, show nicks and divisions in the nucleus, for the most part not like those occurring in the ordinary development of the polymorphonuclear leucocyte. The most striking feature about the specimen is the almost absolute lack of granules. Scarcely a single element containing undoubted neutrophilic granules has been found. After considerable search a single eosinophile was seen. The mononuclear elements consist of typical small lymphocytes with deeply staining nuclei, which nearly fill the cell body, and of elements larger than these all the way up to bodies larger than the ordinary polymorphonuclear cells. These, as has been said, show in many instances nicks which are sometimes deep, so as occasionally almost to divide the nucleus in half. On account of their general similarity in character to the larger mononuclear cells, these have all been classed as mononuclear elements. The protoplasm of some of these elements is deeply staining, of a brownish or slightly lilac color, of others with grayish, and of others nearly colorless. The number of cells with nuclei like those of the ordinary polymorphonuclear leucocyte was small. A differential count of a thousand leucocytes showed: Typical small lymphocytes, 16 per cent.; mononuclear elements smaller than the ordinary polymorphonuclear leucocyte, usually with palely staining nucleus, some showing nicks as above referred to, 22.4 per cent.; cells as large as polymorphonuclear leucocytes or larger, with a nucleus usually palely staining, 55.6 per cent.; cells with distinct polymorphous nucleus, and some showing a suggestion of granulation, but no positive neutrophilic granules, 6 per cent. No nucleated reds or eosinophiles were found among the thousand counted."

An analysis of this case has been puzzling to me. At the time of its observation my notion was that, on admission to the hospital, it was one of scurvy, that typhoid infection had then occurred, and that the acute leukæmia had appeared as a complication of the presumed typhoid fever. The patient had been ailing for two or three months, and on admission her gums were spongy, much swollen, and hemorrhagic, and the teeth loose. Yet several inspections of the blood by Dr. Ghriskey, whose careful technique is well known, showed an evident leukopænia. It is well known that in ordinary spleno-medullary leukæmia there may be periods in the course of the disease in which, with or without extensive splenic enlargement persisting, the leucocytes approach the normal in number, or even fall below, and that the separation of such a case from ordinary splenic anæmia must be made by the persistence of myelocytes in considerable number. Ordinarily, lymphatic leukæmia is acute in onset and course. In the less common chronic cases there are, I believe, no observations showing the intercurrent existence of periods in which the leucocytes diminish to normal or fall below, and in which a high percentage of lymphocytes persists. With glandular enlargement evident, such a case would be indistinguishable from Hodgkin's disease, in certain cases of which there may be an increased percentage of lymphocytes without the total number of leucocytes being above the normal. In the present case it is difficult to conceive lymphatic leukæmia without leucocytosis and without evident external glandular enlargement, which in this case did not exist on admission, and only occurred toward the termination of the case. There, then, was moderate swelling of the cervical, axillary, and inguinal glands. In the present case I am forced to conceive a preleukæmic blood state in which, without leucocytosis, if a differential count had been made on admission, a high percentage of lymphocytes would probably have been found to exist. But as a lymphocytosis may occur in scurvy, the diagnosis of possible leukæmia would have been favored less by this than by the febrile temperature and the lack of prompt improvement in the case under an anti-scorbutic regimen. The woman was of the lower class; had for years overtaxed her strength and had been ill-nourished. She had just passed through gestation and a month of lactation, so that the conditions were favorable for the development of any morbid blood state. Bearing in mind the aping of the clinical picture of typhoid fever by acute leukæmia, it is still conceivable, though not altogether probable, that this patient had, preceding the development of undoubted acute leukæmia, a typhoid infection. Certainly spots appeared which were regarded as similar to those of typhoid,[1] and the blood was reported by Dr. A. H. Stewart, of the City Laboratory, who has had an extensive experience in such examinations, to give the typical Widal reaction.[2]

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[1] But of the minute character of which no record exists, as the condition then was thought to be typhoid fever.

[2] The Widal reaction was examined for but once, and from a dried blood specimen. We had not then begun such examinations at the hospital.

Unfortunately, cultures were not made in life or after death to determine the existence of the typhoid organism. The importance of such cultures was recognized. They were requested repeatedly, but in the very large amount of detailed labor then thrown on Dr. Ghriskey in the organization of the clinical laboratory, then in its incipiency, and who was working without an assistant, they were omitted.*

The post-mortem picture was that of an acute severe infection. The ulcers, the erosion of a vessel of one of which had caused the fatal hemorrhage, were limited to the colon. Dr. Thayer's report of the blood condition is especially interesting, in that it shows the case to belong to a type of very acute malignant leukæmia. This argues against the existence of the disease nearly four months before, at the time of the appearance of spongy gums, and with the absence of a leucocytosis on admission to the hospital a month before. My own judgment is, viewing these and other facts in the case, that the leukæmia was but in its incipiency on admission; that it had very acute onset, with the gradual rise in temperature suggestive of typhoid fever; that the earlier conditions represented a blood dyscrasia allied to scurvy, upon which the very acute and fatal leukæmia was subsequently engrafted.

TYPHOID CHOLECYSTITIS, WITH OBSERVATIONS UPON GALLSTONE FORMATION.†

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Although cholecystitis occurring as a complication of typhoid fever was recognized by Louis, it has not been carefully studied until recent years. In this country the important monographs published in 1897 by Drs. Osler[1] and Mason[2] have directed attention to this serious and not uncommon complication.

We are realizing more and more the important rôle the typhoid bacillus plays in producing pathological processes in various organs and tissues, and the list of the complications and sequelæ of typhoid fever due to the specific bacillus is still increasing.

It was not until 1887 that it was definitely known that Eberth's bacillus could produce a suppurative inflammation. In that year A.

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* The hospital at this time was much overcrowded. Beside the usual run of cases, there were, coincidently, seventy-eight cases of typhoid fever. This service naturally entailed, both on myself, Dr. Ghriskey, and the residents, an excessive amount of routine work, and more than could be adequately well done.

† Read at the first annual meeting of the American Association of Pathologists and Bacteriologists, Boston, 1901.